## REMARKS

Applicants thank the Examiner for the thorough consideration given the present application.

Claims 16, 28 and 78-93 are pending in this application. Claims 16 and 28 are withdrawn from further consideration. Claims 1, 5, 6, 10-13, 27 and 29-77 are currently cancelled; claims 16, 28 and 78 are amended; and new claims 79-93 are added. No new matter has been added. For instance, withdrawn claim 16 changes its dependency from claim 13 to claim 85; withdrawn claim 28 is supported by previous claim 78; amended claim 78 is substantially the same with original version except for numbers 1) -3); new claim 79 is supported by previous claim 10; new claim 80 is supported by previous claim 75; new claim 81 is supported by previous claim 5; new claim 82 is supported by previous claim 6; new claim 83 is supported by previous claim 27; new claim 84 is supported by previous claim 72; new claim 85 is supported by previous claim 13; new claim 86 is supported by previous claim 76; new claim 87 is supported by previous claim 77; new claims 88-90 are supported by claims 78-80 except for the transitional phrase "consisting of"; and new claim 91 is supported by at least page 4, lines 8-18 of the specification. Thus, no new matter is added.

In view of the following remarks, reconsideration of this application is respectfully requested.

### Issue under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1, 5, 6, 10-13, 27, 72, 73 and 75-78 under 35 U.S.C. § 103(a) as being obvious over Gao et al. (USP 6,531,139; hereinafter "Gao") for the grounds as noted at pages 5-10 of the current Office Action.

*The Present Invention and its Advantages*

While not conceding to the Examiner's rejection, independent claim 78 is amended to further emphasize the distinctions of the present invention. Also, new independent claims 79 and 80 are added. Specifically, **claim 78** of the present invention is directed to a solubilized paclitaxel composition consisting essentially of: 1) 40 to 89.9% by weight of monoolein, 2) 10 to 59.99% by weight of an oil chosen from triglyceride, iodized oil, vegetable oil and animal oil, and 3) 0.01 to 10% by weight of paclitaxel. Also, **new claim 79** of the present invention is directed to a solubilized paclitaxel composition consisting essentially of: 1) 40 to 89.9% by weight of monoolein, 2) 10 to 59.99% by weight of an oil chosen from triglyceride, iodized oil, vegetable oil and animal oil, and 3) 0.01 to 10% by weight of paclitaxel, and 4) 0.01 to 5 % by weight of additive, wherein the additive is selected from the group consisting of an anticancer drug, a p-glycoprotein and a hepatic metabolism blocker. Further, **new claim 80** of the present invention is directed to a solubilized paclitaxel composition consisting essentially of: 1) 40 to 89.9% by weight of monoolein, 2) 10 to 59.99% by weight of an oil chosen from triglyceride, iodized oil, vegetable oil and animal oil, 3) 0.01 to 10% by weight of paclitaxel, and 4) 0.01 to 90% by weight of at least one emulsifier.

In the oral paclitaxel formulation field, precipitation of paclitaxel is one obstacle because this precipitate cannot be properly absorbed into the body. Also, another obstacle of paclitaxel formulation is the lower bioavailability of paclitaxel due to an efflux system of p-glycoprotein in the gastrointestinal tract.

However, the present invention solves these problems by the using a combination of monoolein and an oily component along with paclitaxel (see at least pages 4 and 5 and the Examples of the present specification).

*Distinctions between the Present Invention and the Cited Gao Reference*

Gao provides a pharmaceutical composition based on the use of a particular oil phase which comprises 1) a lipophilic, pharmaceutically active agent, 2) a glyceride mixture consisting essentially of diglyceride and monoglyceride, 3) one or more pharmaceutically acceptable

solvents, and 4) one or more pharmaceutically acceptable surfactants. Specifically, Gao's composition focuses on using a mixture of **diglyceride** and monoglyceride in a ratio of from about 9:1 to about 6:4 by weight (diglyceride : monoglyceride). See the Examples of Gao. It means that diglyceride is an essential component to the Gao composition.

However, the claimed composition is not rendered obvious in view of the Gao reference for at least follow reasons.

**(1)** The presently claimed invention employs the language "consisting essentially of", which excludes the diolein and/or solvent ingredients of Gao.

**(i)** In order to arrive at the present invention, one skilled in the art would have to eliminate diglyceride and solvent from the Gao's composition and add the oil (such as triglyceride) of the present invention. However, these are substantially impossible because artisans would not be led to remove such essential ingredients from Gao in a way to destroy the pharmaceutical mechanism thereof.

**(ii)** In addition, as demonstrated in the attached Declaration, the diolein of Gao materially affects the basic and novel properties of the present invention. Specifically, Example 44 of Gao uses paclitaxel, ethanol/polyethyleneglycol (1:1), Cremophor EL and diolein/monoolein (8:2). More specifically, Applicants exactly replicated Example 44 of Gao according to the disclosure of Gao as follows:

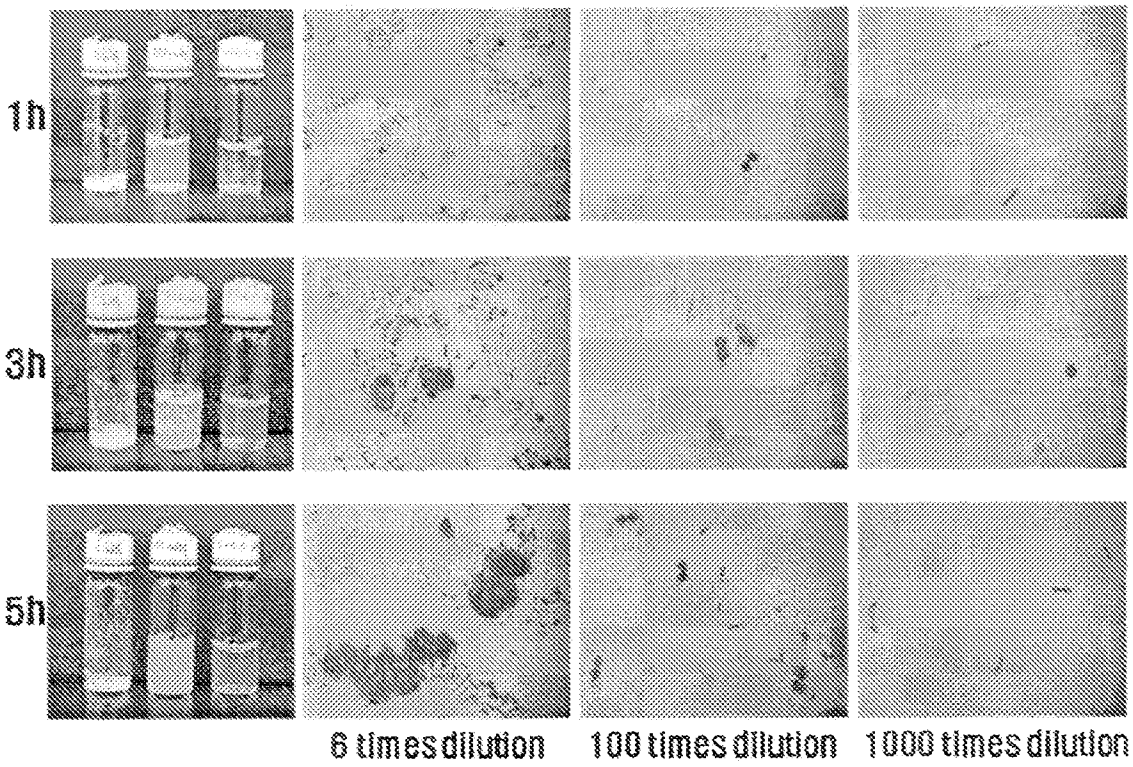
| Component | Weight (mg/g) | % W/W |
|---|---|---|
| Paclitaxel | 60 | 6 |
| EtOH/PEG 400 (1:1) | 300 | 30 |
| Cremophor EL | 440 | 44 |
| Diolein/Monoolein (8:2) | 200 | 20 |

However, Gao does not disclose or suggest any experimental results as to whether Example 44 of Gao could effectively solvate paclitaxel. Thus, Applicants conducted the relevant experiment and presented the results thereof in the attached Declaration.

In such an experiment, it is noted that if the precipitation of a drug (i.e., paclitaxel) occurs when the formulation of the drug is put in contact with water, such formulation is not suitable for use in an oral administration mode. The precipitation of the drug upon contact with water means that the drug is unable to be absorbed into the body, and the bioavailability is thus poor. Therefore, it is very important to find if the precipitation of paclitaxel occurs when it is put in contact with water.

Based on the above, in order to determine the bioavailability of Gao, the compound of Example 44 of Gao was diluted with water, by which the formulation was put in contact with water. As a result, the precipitation of paclitaxel was notably observed. See the below Figure 1 of the Declaration.

**[Figure 1]**




As noted from the above, paclitaxel precipitation was observed in all samples of Gao. Paclitaxel was precipitated into needle type crystals. In particular, as soon as the compound was diluted, paclitaxel precipitation was observed.

On the contrary, the precipitation of pacliaxel was NOT observed in the formulation of the present invention. In this respect, see the Examples of the present specification where no precipitation was observed. Thus, such experimental results lead to the following conclusions:

*(a)* Gao's formulation is not suitable for the oral administration mode of paclitaxel. Although Gao discloses the formulation of paclitaxel as in Example 44, the precipitation of paclitaxel after contact with water shows that bioavailability was not as high as in the present invention. Therefore, the present invention provides superior effects to Gao.

*(b)* As explained above, since Gao using the mixture of diolein and monoolein is not suitable for the oral route, if diolein of Gao would be combined into the present monoolein, such mixture would materially affect the present composition, preventing from using it for the oral route. Thus, the present language "consisting essentially of" removes such diolein ingredient. Therefore, the present invention is patentably distinct from Gao.

**(2)** The Examiner asserts at page 9 of the Office Action that the Gao reference reads on the limitation of claim 1 since **mono**glyceride:**di**glyceride ratio of 6:4 is the equivalent of a 1.5:1 ratio.

However, Applicants respectfully disagree. In the Abstract and claim 1 of Gao, a ratio of **di**glyceride:**mono**glyceride is disclosed as ranging from 9:1 to 6:4. Thus, the monoglyceride:diglyceride ratio (reversal of diglyceride:monoglyceride ratio) is 1:9 to 4:6. Therefore, the monoglyceride:diglyceride ratio of Gao cannot exist at either 6:4 or 1.5:1. In other words, the amount of monoglyceride cannot be greater than that of diglyceride in Gao. In this respect, see also the Examples of Gao wherein the amount of diglyceride should be greater than than that of monoglyceride.

Also, the Examiner asserts at pages 6 and 7 of the Office Action that a person of skill in the art can modify the amounts and/or ratio of the ingredients and the amount of each parameter with respect to the claimed composition is a result-effective parameter that a person having ordinary skill in the art would routinely optimize.

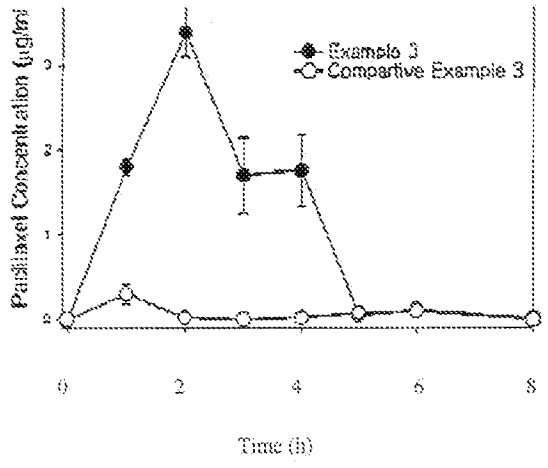
However, as evidenced by the Declaration, when a ratio of diglyceride : monoglyceride ranges within 9:1 to 6:4 (especially 8:2 as in Example 44 of Gao), the bioavailability of paclitaxel is low and also the formulation of Gao is found not to be suitable for the oral route.

Furthermore, the present invention has nothing to do with using diolein of Gao in terms of its intended purpose.

Therefore, the components and ratios of the present invention are different from those of Gao, and the present invention cannot be compared with Gao.

(3) Nevertheless, even if it is assumed that the diglyceride of Gao could be substituted with the present triglyceride, the ratio of triglyceride:monoglyceride ratio in that case is more than 1.5:1. However, since monoolein has high mucoadhesive property, so it is important that monoolein should be a major component in the present invention.

To further establish this point, *in-vivo* oral experimentation procedures similar to Example 12 of the specification were carried out with Comparative Example 3 of the specification (which does not comprise monoolein, but rather paclitaxel, triglyceride and emulsifier). Example 3 of the present invention utilizes paclitaxel, monoolein, tricaprylin and surfactant (Tween). Comparative results thereof are provided in this Reply. According to such results, Comparative Example 3 was not absorbed under oral administration. The results are as follows:



From such results, it is noted that monoolein should be a major component. Therefore, one skilled in the art would not be led to the present invention in which monoolein is a major compound because Gao teaches that the amount of diglyceride is higher than that of monoolein.

**(4)** Further, Applicants wish to point out that the form of the present composition is different from that of Gao. According to page 4, lines 8-18 of the original specification, the composition of the present invention is coarsely dispersed in water, and the absorbance at 400 nm is above 0.38 in all cases and between 1 and 4 in most cases. Briefly, the present composition does not disperse well to the extent of nano-sized particles. Rather, the present composition disperses to form particles of a few micrometers in size.

On the contrary, Gao teaches at column 6, lines 46-55 that Gao's composition is "self-emulsifying formulation," which means a concentrated composition capable of generating emulsions or microemulsions upon mixing with sufficient aqueous media. Also, Gao teaches that microemulsions are characterized by small average droplet size, generally less than about 0.15 micron (150 nm). Thus, it is apparent that Gao discloses a composition capable of preparing nano-sized particles or its pre-concentrates. However, since the present composition is incapable of doing so due to the coarse dispersion in water, the composition of the present invention is further distinguished from Gao.

**(5)** Finally, the composition of the present invention is a lipid-based oral paclitaxel formulation as recited in claims 88-90. A lot of effort has been made in the art to prepare nano-sized particles or a preconcentrates to solubilize paclitaxel, whereas the composition of the present invention does not disperse well and does disperse to form particles of a few micrometers in size. Generally, it is well-known in the prior art that a formulation for paclitaxel should be dispersed well to form nano-sized particles for oral administration because of the low solubility of parclitaxel. In this light, the technical concept of the present invention is contrary to the prior art.

Nonetheless, as is shown by the attached Article (Mol Cancer Ther 2007; 6(12); 3239-3247) which is authored by the inventors of the present invention, the composition of the present invention has excellent oral bioavailabilty.

(6) As the MPEP directs, all the claim limitations must be taught or suggested by the prior art to establish a *prima facie* case of obviousness. *See* MPEP § 2143.03. In view of the fact that the cited reference fails to teach or fairly suggest the claimed features, a *prima facie* case of obviousness cannot be said to exist. Alternatively, it is submitted that the evidence shown in the attached Declaration as well as Article rebuts the *prima facie case* of obviousness.

In light of the above remarks, since the amended independent claims 78-80 of the present application are believed to overcome the 35 USC § 103(a) rejection, the dependent claims therefrom are also believed to be patentable. Therefore, the Examiner is respectfully requested to withdraw this rejection and allow the pending application.

**Issue under 35 U.S.C. § 112, second paragraph**

The Examiner has rejected claim 77 under 35 U.S.C. § 112, second paragraph, due to a certain indefiniteness. This rejection is respectfully traversed.

By way of the present submission, claim 77 is cancelled. Thus, this rejection is moot. Reconsideration and withdrawal thereof are respectfully requested.

**Request for Rejoinder**

Applicants hereby request that the withdrawn claims 16 and 28 be rejoined upon allowance of claim 78.

Specifically, such withdrawn claims 16 and 28 include all the limitation of claim 78. Therefore, rejoinder of these claims 16 and 28 is requested upon allowance.

## Conclusion

In view of the above remarks, Applicants believe the application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Craig A. McRobbie, Reg. No. 42,874 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Dated: JUN 0 9 2010

Respectfully submitted,

By _____

Craig A. McRobbie
Registration No.: 42,874
BIRCH, STEWART, KOLASCH & BIRCH, LLP
8110 Gatehouse Road
Suite 100 East
P.O. Box 747
Falls Church, Virginia 22040-0747
(703) 205-8000
Attorney for Applicants

Attachments: 1. Rule .132 Declaration
2. Article (Mol Cancer Ther 2007: 6(12); 3293-3247)



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